NTP TECHNICAL REPORT

ON THE

# TOXICOLOGY AND CARCINOGENESIS

# STUDIES OF

# GALLIUM ARSENIDE

(CAS NO. 1303-00-0)

# IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

September 2000

NTP TR 492

NIH Publication No. 00-3951

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

## FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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# CONTRIBUTORS

## National Toxicology Program
*Evaluated and interpreted results and reported findings*

J.H. Roycroft, Ph.D., Study Scientist
J.R. Bucher, Ph.D.
R.E. Chapin, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.A. Herbert. D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
D.P. Orzech, M.S.
G.N. Rao, D.V.M., Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., Integrated Laboratory Systems, Inc.

## Battelle Pacific Northwest Laboratories
*Conducted studies, evaluated pathology findings*

B.J. Chou, D.V.M., Ph.D., Principal Investigator
J.A. Dill, Ph.D.
S.L. Grumbein, D.V.M., Ph.D.
T.J. Mast, Ph.D.
P.W. Mellick, D.V.M., Ph.D.
K. Mellinger, M.S.
R.A. Miller, D.V.M., Ph.D.
H.A. Ragan, D.V.M.
R.A. Renne, D.V.M.
Y.F. Su, Ph.D.
R.B. Westerberg, Ph.D.

## Experimental Pathology Laboratories, Inc.
*Provided pathology quality assurance*

J.F. Hardisty, D.V.M., Principal Investigator
C.C. Shackelford, D.V.M., M.S., Ph.D.

## Dynamac Corporation
*Prepared quality assurance audits*

S. Brecher, Ph.D., Principal Investigator

## NTP Pathology Working Group
*Evaluated slides, prepared pathology report on rats (3 September 1998)*

P.K. Hildebrandt, D.V.M., Chairperson
PATHCO, Inc.
R. Cattley, V.M.D., Ph.D.
Chemical Industry Institute of Toxicology
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
S.L. Grumbein, D.V.M., Ph.D.
Battelle Pacific Northwest Laboratories
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
M.P. Jokinen, D.V.M.
Pathology Associates International
A. Nyska, D.V.M.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.

*Evaluated slides, prepared pathology report on mice (23 July 1998)*

P.K. Hildebrandt, D.V.M., Chairperson
PATHCO, Inc.
R. Cattley, V.M.D., Ph.D.
Chemical Industry Institute of Toxicology
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
R.A. Miller, D.V.M., Ph.D.
Battelle Pacific Northwest Laboratories
A. Nyska, D.V.M.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.

**Analytical Sciences, Inc.**
*Provided statistical analyses*

R.W. Morris, M.S., Principal Investigator
D.E. Kendrick, M.S.
K.P. McGowan, M.B.A.
J.T. Scott, M.S.

**Biotechnical Services, Inc.**
*Prepared Technical Report*

S.R. Gunnels, M.A., Principal Investigator
L.M. Harper, B.S.
A.M. Macri-Hanson, M.A., M.F.A.
P.A. Yount, B.S.

# CONTENTS

# ABSTRACT

# GaAs

**GALLIUM ARSENIDE**

CAS No. 1303-00-0

Molecular Formula: GaAs Molecular Weight: 144.64

**Synonym:** Gallium monoarsenide

Gallium arsenide is used primarily to make light-emitting diodes, lasers, laser windows, and photodetectors and in the photoelectronic transmission of data through optical fibers. Gallium arsenide was nominated for study because of its widespread use in the microelectronics industry, the potential for worker exposure, and the absence of chronic toxicity data. Male and female F344/N rats and $B6C3F_1$ mice were exposed to gallium arsenide particles (greater than 98% pure; mass median aerodynamic diameter = 0.8 to 1.0 $\mu$m) by inhalation for 16 days, 14 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, and the frequency of micronuclei was determined in the peripheral blood of mice exposed to gallium arsenide for 14 weeks.

## 16-DAY STUDY IN RATS

Groups of five male and five female rats were exposed to particulate aerosols of gallium arsenide with a mass median aerodynamic diameter of approximately 1 $\mu$m at concentrations of 0, 1, 10, 37, 75, or 150 mg/m$^3$ by inhalation, 6 hours per day, 5 days per week, for 16 days. All rats survived to the end of the study. The final mean body weights of all exposed groups of males and females were similar to those of the chamber controls. Compared to chamber controls, the liver and lung weights of males exposed to 1 mg/m$^3$ or greater and females exposed to 10 mg/m$^3$ or greater were increased; the thymus weights of all exposed groups of males were decreased. Gallium arsenide particles were visible in the alveolar spaces and, to a lesser extent, within alveolar macrophages of exposed rats. Moderate proteinosis (surfactant mixed with small amounts of fibrin) and minimal histiocytic cellular infiltrate were observed in the alveoli of exposed males and females. Epithelial hyperplasia and squamous metaplasia of the larynx were observed primarily in males exposed to 150 mg/m$^3$.

## 16-DAY STUDY IN MICE

Groups of five male and four or five female mice were exposed to particulate aerosols of gallium arsenide with a mass median aerodynamic diameter of approximately 1 $\mu$m at concentrations of 0, 1, 10, 37, 75, or 150 mg/m$^3$ by inhalation, 6 hours per day, 5 days per week, for 16 days. The final mean body weights were similar among exposed and chamber control groups. Compared to chamber controls, the lung weights of males and females exposed to 10 mg/m$^3$ or greater were increased. Gallium arsenide particles were visible in alveolar spaces and macrophages in some mice exposed to 150 mg/m$^3$. Moderate proteinosis, mild epithelial hyperplasia, and histiocytic infiltration of the lung were observed in males and females exposed to 10 mg/m$^3$ or greater. In the larynx, mild squamous metaplasia was seen in mice exposed to 10 mg/m$^3$ or greater, and mild

chronic inflammation occurred in mice exposed to 75 or 150 mg/m$^3$.

## 14-Week Study in Rats

Groups of 10 male and 10 female rats were exposed by inhalation to gallium arsenide particulate at concentrations of 0, 0.1, 1, 10, 37, or 75 mg/m$^3$, 6 hours per day, 5 days per week, for 14 weeks. All rats survived until the end of the study. The final mean body weight and body weight gain of males exposed to 75 mg/m$^3$ were significantly less than those of the chamber controls.

Hematology and clinical chemistry results indicated that exposure to gallium arsenide induced a microcytic responsive anemia with an erythrocytosis and increased zinc protoporphyrin/heme ratios in exposed groups of rats. There were also increases in platelet and neutrophil counts, a transient decrease in leukocyte counts, and increases in the serum activities of alanine aminotransferase and sorbitol dehydrogenase. These changes were of greater magnitude in male rats. The lung weights of all exposed groups of rats were increased, while testis, cauda epididymis, and epididymis weights of males exposed to 37 or 75 mg/m$^3$ were generally less than those of chamber controls. Total spermatid heads and spermatid counts were significantly decreased in males exposed to 75 mg/m$^3$, while epididymal spermatozoa motility was significantly reduced in males exposed to 10 mg/m$^3$ or greater.

Gallium arsenide particles were visible in alveolar spaces and macrophages in the lungs of exposed rats. Minimal to marked proteinosis and minimal histiocytic cellular infiltration of the alveoli were observed in all exposed groups; minimal squamous metaplasia in the larynx and lymphoid cell hyperplasia of the mediastinal lymph node were observed in some males and females exposed to 37 or 75 mg/m$^3$. Exposure-related increases in the incidences of plasma cell hyperplasia of the mandibular lymph node, testicular atrophy, epididymal hypospermia, bone marrow hyperplasia (males), and hemosiderosis in the liver were observed in the 37 and 75 mg/m$^3$ groups.

## 14-Week Study in Mice

Groups of 10 male and 10 female mice were exposed by inhalation to gallium arsenide particulate at concentrations of 0, 0.1, 1, 10, 37, or 75 mg/m$^3$, 6 hours per day, 5 days per week, for 14 weeks. One female mouse exposed to 75 mg/m$^3$ died before the end of the study. Final mean body weights and body weight gains of males in the 75 mg/m$^3$ group were significantly less than the chamber controls.

Hematology and clinical chemistry results indicated that exposure to gallium arsenide affected the circulating erythroid mass and induced a microcytic responsive anemia with an erythrocytosis and increased zinc protoporphyrin/heme ratios in male and female mice. There were also increases in platelet and neutrophil counts. Compared to the chamber controls, the lung weights of males exposed to 1 mg/m$^3$ or greater and females exposed to 10 mg/m$^3$ or greater were increased. Testis, cauda epididymis, and epididymis weights, total spermatid heads, spermatid counts, and concentration and motility of epididymal spermatozoa were generally decreased.

Gallium arsenide particles were visible in alveolar spaces and macrophages in the lungs of mice exposed to 1 mg/m$^3$ or greater. Mild to marked proteinosis, histiocytic infiltration, and epithelial hyperplasia were observed in the alveoli of males and females exposed to 1 mg/m$^3$ or greater. Minimal to mild suppurative inflammation and granuloma in the lung and squamous metaplasia in the larynx were present in males and females exposed to 10 mg/m$^3$ or greater. Minimal hyperplasia was observed in the tracheobronchial lymph node of males exposed to 10 mg/m$^3$ or greater and females exposed to 37 or 75 mg/m$^3$. Exposure-related increases in the incidences of testicular atrophy, epididymal hypospermia, hematopoietic cell proliferation of the spleen, and hemosiderosis of the liver and spleen were observed in groups of male and female mice exposed to 10 mg/m$^3$ or greater.

## 2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed by inhalation to gallium arsenide particulate at concentrations of 0, 0.01, 0.1, or 1.0 mg/m$^3$, 6 hours per day, 5 days per week, for 105 weeks.

### *Survival and Body Weights*

Survival of exposed male and female rats was similar to the chamber controls. Mean body weights of males exposed to 1.0 mg/m$^3$ were generally less than those of the chamber controls throughout the study; females

exposed to 1.0 mg/m$^3$ had slightly lower mean body weights during the second year.

### *Pathology Findings*

Compared to the chamber controls, the incidences of alveolar/bronchiolar neoplasms were significantly increased in females exposed to 1.0 mg/m$^3$ and exceeded the historical control ranges. Exposure-related nonneoplastic lesions in the lungs of male and female rats included atypical hyperplasia, alveolar epithelial hyperplasia, chronic active inflammation, proteinosis, and alveolar epithelial metaplasia. In the larynx of males exposed to 1.0 mg/m$^3$, the incidences of hyperplasia, chronic active inflammation, squamous metaplasia, and hyperplasia of the epiglottis were significantly increased.

The incidences of benign pheochromocytoma of the adrenal medulla occurred with a positive trend in female rats, and the incidence was significantly increased in the 1.0 mg/m$^3$ group and exceeded the historical control range.

The incidence of mononuclear cell leukemia was significantly increased in females exposed to 1.0 mg/m$^3$ and exceeded the historical control range.

## 2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were exposed by inhalation to gallium arsenide particulate at concentrations of 0, 0.1, 0.5, or 1.0 mg/m$^3$, 6 hours per day, 5 days per week, for 105 (males) or 106 (females) weeks.

### *Survival and Body Weights*

Survival of male and female mice was similar to the chamber controls. Mean body weights of exposed groups of males were similar to those of the chamber controls throughout the study; mean body weights of exposed groups of females were greater than those of the chamber controls from week 13 until the end of the study.

### *Pathology Findings*

Exposure-related nonneoplastic lesions in the lung of all groups of exposed mice included suppurative focal inflammation, chronic focal inflammation, histiocyte cellular infiltration, alveolar epithelial hyperplasia, and proteinosis. Increased incidences of minimal lymphoid hyperplasia of the tracheobronchial lymph node occurred in mice exposed to 1.0 mg/m$^3$ and in 0.5 mg/m$^3$ males.

## GENETIC TOXICOLOGY

Gallium arsenide was not mutagenic in several strains of *Salmonella typhimurium*, with or without S9 metabolic activation enzymes, and no increase in the frequency of micronucleated erythrocytes was observed in peripheral blood of male or female mice exposed to gallium arsenide by inhalation for 14 weeks.

## CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of gallium arsenide in male F344/N rats exposed to 0.01, 0.1, or 1.0 mg/m$^3$. There was *clear evidence of carcinogenic activity* in female F344/N rats based on increased incidences of benign and malignant neoplasms in the lung. Increased incidences of benign neoplasms of the adrenal medulla and increased incidences of mononuclear cell leukemia were also considered to be exposure related. There was *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice exposed to 0.1, 0.5, or 1.0 mg/m$^3$.

Exposure to gallium arsenide caused a spectrum of nonneoplastic lesions in the lungs of rats and mice and the larynx of male rats and hyperplasia of the tracheobronchial lymph node in mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A Summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Gallium Arsenide**

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Concentrations in air** | 0, 0.01, 0.1, or 1.0 mg/$m^3$ | 0, 0.01, 0.1, or 1.0 mg/$m^3$ | 0, 0.1, 0.5, or 1.0 mg/$m^3$ | 0, 0.1, 0.5, or 1.0 mg/$m^3$ |
| **Body weights** | 1.0 mg/$m^3$ group generally less than chamber control group | 1.0 mg/$m^3$ group slightly less than chamber control group | Exposed groups similar to chamber control group | Exposed groups generally greater than chamber control group |
| **Survival rates** | 13/50, 13/50, 15/50, 13/50 | 19/50, 17/50, 21/50, 11/50 | 35/50, 38/50, 34/50, 34/50 | 36/50, 34/50, 31/50, 29/50 |
| **Nonneoplastic effects** | Lung: hyperplasia, atypical (0/50, 2/49, 5/50, 18/50); alveolar epithelium, hyperplasia (12/50, 16/49, 21/50, 21/50); inflammation, chronic, active (3/50, 43/49, 50/50, 50/50); proteinosis (0/50, 22/49, 50/50, 49/50); alveolar, epithelium, metaplasia (0/50, 2/49, 34/50, 41/50)<br><br>Larynx: hyperplasia (3/50, 8/50, 4/49, 11/50); inflammation, chronic, active (4/50, 3/50, 4/49, 12/50); metaplasia, squamous (1/50, 2/50, 2/49, 10/50); epiglottis, hyperplasia (0/50, 6/50, 4/49, 5/50) | Lung: hyperplasia, atypical (0/50, 0/50, 9/50, 15/50); inflammation, chronic active (11/50, 46/50, 49/50, 50/50); proteinosis (1/50, 24/50, 47/50, 49/50); alveolar epithelium, metaplasia (0/50, 1/50, 36/50, 41/50) | Lung: inflammation, focal suppurative (0/50, 0/50, 8/50, 23/50); inflammation, chronic, focal (1/50, 3/50, 3/50, 12/50); infiltration cellular, histiocyte (3/50, 10/50, 45/50, 48/50); alveolar epithelium, hyperplasia (4/50, 9/50, 39/50, 45/50); alveolus, proteinosis (1/50, 4/50, 49/50, 50/50)<br><br>Lymph Node, Tracheobronchial: hyperplasia (5/38, 7/37, 17/40, 24/41) | Lung: inflammation, focal suppurative (0/50, 0/50, 2/50, 14/50); inflammation, chronic, focal (1/50, 2/50, 11/50, 18/50); infiltration cellular, histiocyte (2/50, 13/50, 48/50, 49/50); alveolar epithelium, hyperplasia (2/50, 5/50, 27/50, 43/50); alveolus, proteinosis (0/50, 4/50, 49/50, 50/50)<br><br>Lymph Node, Tracheobronchial: hyperplasia (10/39, 12/43, 13/42, 23/42) |
| **Neoplastic effects** | None | Lung: alveolar/bronchiolar adenoma (0/50, 0/50, 2/50, 7/50); alveolar/bronchiolar carcinoma (0/50, 0/50, 2/50, 3/50); alveolar/bronchiolar adenoma or carcinoma (0/50, 0/50, 4/50, 9/50)<br><br>Adrenal Medulla: benign pheochromocytoma (4/50, 5/49, 6/50, 13/49)<br><br>Mononuclear Cell Leukemia: (22/50, 21/50, 18/50, 33/50) | None | None |

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Gallium Arsenide**

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Level of evidence of carcinogenic activity** | No evidence | Clear evidence | No evidence | No evidence |
| **Genetic toxicology** | | | | |
| *Salmonella typhimurium* gene mutations: | | Negative in strains TA97, TA98, TA100, TA102, and TA1535, with and without S9 | | |
| Micronucleated erythrocytes | | | | |
| Mouse peripheral blood *in vivo*: | | Negative | | |

## EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

## NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
## TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on gallium arsenide on 21 May 1999 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Gary P. Carlson, Ph.D., Chairperson
School of Health Sciences
Purdue University
West Lafayette, IN

A. John Bailer, Ph.D., Principal Reviewer
Department of Mathematics and Statistics
Miami University
Oxford, OH

Steven A. Belinsky, Ph.D., Prinicipal Reviewer
Inhalation Toxicology Research Institute
Kirkland Air Force Base
Albuquerque, NM

James S. Bus, Ph.D.*
Health and Environmental Services
Dow Chemical Company
Midland, MI

Linda A. Chatman, D.V.M.
Pfizer, Inc.
Groton, CT

John M. Cullen, V.M.D., Ph.D.
Department of Microbiology, Parasitology, and Pathology
College of Veterinary Medicine
North Carolina State University
Raleigh, NC

Harold Davis, Ph.D., Principal Reviewer
Director of Toxicology
Amgen, Inc.
Thousand Oaks, CA

Susan M. Fischer, Ph.D.
M.D. Anderson Cancer Center
The University of Texas
Smithville, TX

Stephen S. Hecht, Ph.D.
University of Minnesota Cancer Centers
Minneapolis, MN

Michele Medinsky, Ph.D.
Durham, NC

Jose Russo, M.D.
Fox Chase Cancer Center
Philadelphia, PA

---

*Did not attend

## SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 21 May 1999, the draft Technical Report on the toxicology and carcinogenesis studies of gallium arsenide received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.H. Roycroft, NIEHS, introduced the toxicology and carcinogenesis studies of gallium arsenide by discussing the uses of the chemical, describing the rationale for study and the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic lesions in female rats and nonneoplastic lesions in male and female rats and mice. Additionally, lung burden studies were conducted in male rats from the 14-week and 2-year studies. The proposed conclusions were *no evidence of carcinogenic activity* in male F344/N rats or male or female $B6C3F_1$ mice and *clear evidence of carcinogenic activity* in female F344/N rats.

Dr. Belinsky, a principal reviewer, agreed with the proposed conclusions.

Dr. Davis, the second principal reviewer, agreed with the proposed conclusions. He noted the basis for selecting exposure concentrations in the 2-year rat study as increased severity of lung lesions (proteinosis and inflammation) in the 14-week study; however, inflammation was not increased between the 10 $mg/m^3$ and 1 $mg/m^3$ groups. Dr. Roycroft stated that exposure concentration selection was based primarily on the proteinosis, and this would be clarified in the report. Dr. Davis also asked if neoplasms would have been seen in male rats had higher exposure concentrations been used. Dr. Roycroft agreed that higher exposure concentrations might have been tolerated, but, based on lung weight increases of about 60% in the 14-week study at 1 $mg/m^3$ and the presence of an animal with fibrosis, the highest exposure concentration chosen for the 2-year study was sufficiently challenging. Dr. Davis stated it would be helpful to have a reason why lung burden was not assessed in female rats. Dr. Roycroft replied there were considerable data on absorption of gallium and arsenic in male rats, as well as more experience with particulate studies.

Dr. Bailer, the third principal reviewer, agreed with the proposed conclusions. He thought that in the study design it would have been useful to link typical human occupational exposures to the animal exposure concentrations. In this context, he thought more recent human exposure information should be available. Dr. Roycroft said the 1981 estimate was the best available, but was not specific to gallium arsenide. Dr. M. Toraason, NIOSH, commented that NIOSH was embarking on an effort to reinitiate the National Occupational Exposure Survey, so perhaps more recent exposure data will be available in the future. Dr. Bailer stated that in plots of lung burdens for gallium and arsenic in male rats over time (Figure 8), the superimposed lung deposition and clearance model did not fit the data for the high exposure concentrations for days 150 and beyond, most particularly in the high exposure concentration group at 18 months. Dr. J.R. Bucher, NIEHS, agreed that from a toxicological standpoint the model clearly was inadequate to explain what happened toward the end of the study. He said the interest in following lung burden throughout the study was to determine whether an overload situation was reached. Dr. Bailer observed that neither the data nor the fit of the model suggest an overload phenomenon.

In further discussion, Dr. Medinsky asked about the balance between obtaining complete toxicokinetic information during a chronic study to aid in understanding mechanisms of toxicity versus expeditious reporting of primary toxicologic and carcinogenic information. Dr. G.W. Lucier, NIEHS, agreed that the need to release toxicologic data may sometimes preclude reporting the complete toxicokinetic story. Dr. Russo asked whether the alveolar proteinosis appeared before hyperplasia. Dr. R.A. Herbert, NIEHS, responded that the proteinosis was most prominent in prechronic studies although there was some hyperplasia, while in the 2-year studies, these lesions were seen together in the same animals.

Dr. Belinsky moved that the Technical Report on gallium arsenide be accepted with revisions discussed and the conclusions as written for male rats and male and female mice, *no evidence of carcinogenic activity*, and for female rats, *clear evidence of carcinogenic activity*. Dr. Davis seconded the motion, which was accepted unanimously with nine votes.